REMARKS

1. Response to the Withdrawal of the Finality of the Previous Office Action

Applicant does not understand why the Examiner has continued presenting arguments in support of the finality of the previous office action because the issue is moot. For the record, Applicant maintains the position that the finality of the previous office action was premature for the reasons previously expressed.

2. Objections to the Specification and Claims

Applicant expresses appreciation to the Examiner for pointing out the spelling and grammar errors in the Specification and Claims, as well as, the improper dependency of Claims 9 and 23. Although the errors seem insignificant, Applicant welcomes the opportunity to make the corrections to place the application in further condition for allowance.

3. Amendment to the Claims

Applicant appreciates the Examiner pointing out that in the independent Claims 1 and 16 the term "red blood cell" can potentially include more than one meaning. Applicant recognizes that the first meaning is used to denote the general biological term of red blood cell. Such a use is found in the phrases "progenitor cells of red blood cells" and "non-native to the red blood cells". The second meaning is used to describe the red blood cells produced by the transfected progenitor cells, wherein the produced red blood cells containing the produced protein which is non-native to the red blood cells. To distinguish the two red blood cell meanings for complying with 35 U.S.C. §112, second paragraph, Applicant has used the term of "altered red blood cells" to define the red blood cells produced by the transfected progenitor cells. The same amendment has also been made in the dependent claims of Claims 1 and 16. Applicant respectfully states the above-described amendment does not introduce new matters.

4. Response to Rejection of Claims 1-29 based upon 35 U.S.C. §112, first paragraph

Claims 1-8, 10-21 and 24-29, the remaining pending claims, stand rejected under 35 U.S.C. §112, first paragraph. The Examiner asserts that the claims contain subject matter, which was not described in such a way to enable one skilled in the art to which it pertains to make and/or use the invention. This rejection is respectfully traversed.

The first time this type of rejection was raised occurred in the first Office Action dated October 22, 1999 (Paper No. 3). The rejection was traversed by Applicant's response to the Office Action dated April 20, 2000 (Paper No. 6). The Examiner withdrew the rejection in the second Office Action dated July 17, 2000 (Paper No. 7) stating that Applicant made the statement in prosecution of the claims that "the claimed invention is not intended to be used for gene therapy". Applicant was particularly concerned with prosecution history estoppel and therefore respectfully informed the Examiner that Applicant did not make any such disclaimer. Applicant's response to the rejection was that the claimed invention was directed to the delivery of a protein to the blood in vivo, which the Examiner had previously noted was enabled by the Specification.

The second time that the Examiner raises this rejection is in the present Office Action dated October 25, 2001 (Paper No. 14). In this second rejection, the Examiner's foundation for his rejection is the Examiner's assertion that gene therapy is within the scope of the claimed invention and therefore gene therapy is not enabled.

Applicant respectfully points out that Claim 1 of the present invention is a method for producing and delivering protein in vivo. More specifically, the method produces altered red blood cells containing protein that is non-native to red blood cells, and uses the blood cell rupture to deliver produced protein which is non-native to red blood cells into the blood stream in vivo. Claim 16 of the present invention is a method using a hemoglobin promoter to produce altered red blood cells containing non-hemoglobin protein, and using the blood cell rupture to deliver produced non-hemoglobin protein into blood stream in vivo.

Applicant notes that as defined, the present claimed invention is to a method of producing a protein in the progenitor cells of red blood cells, and delivering produced protein into blood stream by rupture of the red blood cells. From the blood stream, the protein can be delivered to the functional site, which can be directly in the circulating blood, as in the case of human serum albumin and insulin, or to specific organs and tissues. However, Applicant's claimed invention is not a mechanism of protein intake by a specific cell. Furthermore, although the present invention can be used for disease treatment as apparent to one skilled in the art, Applicant claimed invention as defined by the claims is not, nor intended to be, a specific gene therapy protocol.

Applicant is only responsible for enablement of the disclosed method within the scope defined by the claims, not beyond the scope of the claims. As Examiner stated on page 4, line 6 of the first Office Action, the present invention is "enabling for delivery of a protein to the blood in vivo". That is precisely the claimed invention. Therefore, the specification, as filed, satisfies the enablement requirement.

Applicant has truly endeavored to view the present rejection from the Examiner's view. The Examiner appears to have viewed the claimed invention of delivery of a protein to the blood in vivo as the same as a gene therapy protocol.

The Examiner's view is not consistent with an the objective views that:

1) gene therapy is a separate invention from Applicant's claimed mechanism for delivery of a protein. More specifically, a gene therapy can use a different protein delivery mechanism other than Applicant's claimed invention of a specific mechanism for the delivery of a protein. Therefore, Applicant is not required to provide an enablement for the separate invention of gene therapy;

2) Applicant's claimed mechanism for delivery of a protein is separate from an invention directed to the use of the protein in a gene therapy method. More specifically, Applicant's claimed invention of a specific mechanism for the delivery of a protein is only one part of a gene therapy invention. In other words, a process to make a product is separate from the use of the product. Applicant believes that this situation can be analogous to Applicant claiming a method of producing time-release high potency Vitamin C tablets, but Applicant is not responsible for any clinical use of the Vitamin C for treatment of diseases. Therefore, as previously determined, Applicant is not

required to provide an enablement for the separate invention of gene therapy.

Moreover, Applicant further avoided the therapeutic enabling issue by employing an approach that has been readily accepted, as shown in the primary reference, Hollis et al., which was used by the Examiner in further claim rejections. In the Hollis et al. reference, as well as, other protein expression patents, each uses the same strategy of claiming the expression or production of proteins rather than a specific gene therapy protocol. Applicant has adopted this same approach by claiming the delivery of proteins rather a specific gene therapy protocol.

Still further, Applicant admitted in the Specification that:

> After significant progress in the technology of gene therapy, the concept of using gene therapy to cure or alleviate inherited and acquired diseases has been accepted. Investigators have accomplished the requisite first steps: it has been shown that transferred genes can be induced to function in the human body. So far, however, no approach has definitively improved the health of one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide. This lack of a convincing therapeutic benefit may reflect researchers' imperfect initial groping toward a difficult new technology and that the obstacles are more formidable than expected.

Therefore, it is apparent to the Applicant, the Examiner and those skilled in the art that a precise gene therapy protocol is still to be invented. However, using the Examiner's unduly restrictive interpretation, the Examiner is asking Applicant to disclaim by prosecution history estoppel Applicant's ownership of the claimed protein delivery mechanism just because it can be used in a therapeutic procedure. More specifically, if a precise gene therapy protocol was invented which uses Applicant's claimed protein delivery mechanism, then the Examiner's position denies Applicant's inventive rights to Applicant's claimed invention. It is untenable of the Patent Office to refuse granting Applicant a patent on Applicant's discovered mechanism merely because the discovered mechanism is susceptible of further uses.

The Examiner's rejection is simply unfair and not logical to promoting the useful arts. First, the Examiner has agreed that the present invention is "enabling for delivery of a protein to the blood in vivo". (Page 4, line 6 of the first Office Action, Paper No. 3).

Second, Applicant's claimed invention has utility for producing and delivering

proteins in vivo. The present Specification, page 6, provides a host of utilities for Applicant's claimed invention. More specifically:

> One object of the present invention is to provide a non-tissue specific method that utilizes suitable host cells for synthesis of proteins.
>
> Another object of the present invention is to specifically control the expression and production of proteins in the precursors of the red blood cells.
>
> An additional object is to utilize the non nucleated cell nature of the red blood cells to provide an environment that benefits the stability of the proteins after their production.
>
> Yet another object of the present invention is to bypass the secretion and exocytosis pathways for protein release from the manufacturing site.
>
> Another object of the present invention is to use hemoglobin promoter to achieve the control of the expression and synthesis of proteins in the precursors of the red blood cells.

Therefore, Applicant maintains that he has complied with the requirements of 35 U.S.C. §112, first paragraph.

Applicant points out that if gene therapy is to occur, then the research necessary to discover a gene therapy must be supported by the investment community and the investment community views patents as an essential requirement for funding further research. It would be patently unjust to require an applicant to delay seeking patent protection on one method of a mechanism of protein delivery until after the specific gene therapy has been discovered and proven.

Accordingly, Applicant respectfully requests withdrawal of the rejection of Claims 1-8, 10-21 and 24-29, the remaining pending claims, based upon 35 U.S.C. §112, first paragraph.

5. Response to Rejection of Claims 10 and 24 based on 35 U.S.C. §112 first paragraph

Dependent Claims 10 and 24 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the Specification in such a way as to enable one skilled in the art to make and/or use the invention. More specifically, the Examiner asserts that the Specification teaches that the life cycle of red

blood cells can be modified by genetic mutations, but teaches no mutations which would be suitable for this purpose and provides no guidance as to how to obtain cells comprising these mutations. This rejection is respectfully traversed.

Claims 10 and 24, which depend from Claims 1 and 16 respectfully, are narrowed claims to a method of delivering proteins in which red blood cells containing the proteins are induced to rupture in vivo by genetic mutation.

Applicant disclosed in the specification as filed (page 12, line 2) that the life cycle time of red blood cells can be modified by genetic mutation. Applicant made such an example because it is known to those skilled in the art that genetic mutation can cause shortening of red blood cell life time. For instance, spherocytosis and elliptocytosis result from genetic mutation. In both spherocytosis and elliptocytosis, abnormally shaped red blood cells have a shorter lifetime. It is also known to those skilled in the art that mutations of red blood cell enzymes lead to haemolytic anemia.

Applicant submitted copies of two references regarding genetic mutations in Paper No. 6 to illustrate that genetic mutations resulting shortened red blood cell life was well known in the art at the time of filing. Moreover, the Examiner acknowledged that the submitted references "support the position that natural mutations resulting in shortened red blood cell life were well know in the art at the time of filing." Therefore, it is not necessary for Applicant to make available the known mutated genes.

Applicant merely utilized known genetic techniques for producing cells with mutated genes in the claimed inventive method for producing and delivering protein into the blood stream. Therefore, those skilled in the art at the time of the filing of the present patent application would have been able to produce the known mutated genes and cells, without undue experimentation, given the teachings of the Specification along with tools and methods well known in the art. Moreover, Applicant fully disclosed the method of introducing a gene encoding a protein which is non-native to the red blood cells to the progenitor cells of red blood cells in the Specification and in the Example as filed, see page 7 to 9, and page 16 to 18. There would be no undue experimentation required to obtain Applicants claimed induced rupture of red blood cells by genetic mutation.

Accordingly, Applicant respectfully requests withdrawal of the rejection of Claims

10 and 24 based upon 35 U.S.C. §112, first paragraph.

6. Response to Rejection of Claims 16-21 and 23-29 based on 35 U.S.C. §112, first paragraph

Claims 16-21 and 23-29 stand rejected under 35 U.S.C. §112, first paragraph. This portion of the rejection has been obviated by incorporation of the Examiner's suggestions in the Claims. Accordingly, Applicant respectfully requests withdrawal of the rejection of Claims 16-21 and 23-29 based upon 35 U.S.C. §112, first paragraph.

7. Response to Rejection of Claims 1-29 based on 35 U.S.C. §112, second paragraph

Claims 1-8, 10-21 and 24-29, the remaining pending claims, stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. This rejection is respectfully traversed.

After the latest amendments in response to the instant Office Action, Applicant believes that Claims 1-8, 10-21 and 24-29, the remaining pending claims, do in fact particularly point out and distinctly claim the subject matter, which Applicant regards as the invention.

The Examiner is respectfully requested to consider the holding in Beachcombers International, Inc. v. Wildewood Creative Products, Inc. 31 USPQ 2d 1653, 1656 (Fed. Cir. 1994) which held:

> The relevant statute, 35 U.S.C. §112 ¶ 2 (1988), requires that the claims "particularly [point] out and distinctly [claim] the subject matter which the applicant regards as his invention." The operative standard for determining whether this requirement has been met is "whether those skilled in the art would understand what is claimed when the claim is read in light of the specification." Orthokinetices Inc. v. Safety

Travel Chairs Inc., 806 F.2d 1565, 1576, 1 USPQ 2d 1081, 1088 (Fed. Cir. 1986).

The Examiner has raised these new issues only now in this third office action. The Examiner is respectfully requested to provide reasonable rejections. Applicant respectfully believe that the issues should be narrowing rather than expanding in the prosecution of this application.

For example, the Examiner maintains that Claim 3 and 18 are indefinite because it is unclear what is intended by "natural promoter". In this context, Applicant refers the Examiner the Specification, page 8, which defines the natural promoter which is consistent with the use of such word in the prior art as exemplified by Hollis et al., column 2, lines 54 - 63.

Claims 1-8, 10-21 and 24-29, the remaining pending claims, are not indefinite because they do not take on an unreasonable degree of uncertainty when construed in light of the prior art and the disclosure of the Specification.

In In re Tanksley, 37 USPQ 2d 1382, 1386 B.P.A.I. 1994) the Board held:

> In our judgement, a patent applicant is entitled to a reasonable degree of latitude in complying with the second paragraph of 35 U.S. C. §112 and the examiner may not dictate the literal terms of the claims...Stated another way, a patent applicant must comply with 35 U.S.C. §112, second paragraph, but just how the applicant does so, within reason, is within applicant's discretion.

Notwithstanding, Applicant appreciates the Examiner's suggestions as to wording the Examiner would like to see in the claims and Applicant has considered such suggestions and incorporated most of the suggestions which the Examiner has proffered. However, the law is clear about the requirements of 35 U.S.C. §112, second paragraph, that the Applicant particularly points out and distinctly claims the subject matter, which Applicant regards as the invention. Raising these rejections at this time

does not facilitate efficient prosecution of Applicant's patent application and raises concerns about the motive of the Patent Office.

Accordingly, Applicant respectfully requests withdrawal of the rejection of Claims 1-8; 10-21 and 24-29 based upon 35 U.S.C. §112, second paragraph.

8. Response to Rejection of Claims 1-5, 8, 9, 16-19, 23 and 25-27 Based Upon 35 U.S.C. §102(b)

Claims 1-5, 8, 16-19, 23 and 25-27 stand rejected under 35 U.S.C. §102(b) as being anticipated by Hollis et al (US Patent 5,538,885). This rejection is respectfully traversed.

Hollis et al teach expression systems which comprise a mammalian host transformed with a vector which comprises a promoter, and a DNA sequence which codes for a desired polypeptide and a dominant control region. Further, Hollis et al teach that the expression systems are capable of expressing a polypeptide at high levels and secreting the polypeptide expressed.

More specifically, Hollis et al demonstrate in Example 3 the long term secretion of human growth hormone (HGH) over a period of 80 days in vitro (column 14, line 47 to column 15, line 25). To confirm the mechanism of the protein delivery, Hollis et al further demonstrate in Example 4 that no increase in supernatant HGH levels in the presence of a secretion inhibitor, brefeldin-A, which is known specifically blocking flux through the Golgi apparatus. Hollis et al conclude, therefore, "the appearance of HGH in the supernatant is due to the secretion of the protein through the Golgi apparatus".

Applicant's claimed invention is a method for producing and delivering protein in vivo, which comprises inserting into a vector a promoter and a gene encoding a non-native protein to red blood cells, wherein the promoter is active only in the progenitor cells of red blood cells; collecting an amount of progenitor cells of red blood cells from a mammal; transfecting the progenitor cells of red blood cells in vitro with the vector containing the promoter and the gene; introducing the transfected progenitor cells of red blood cells back to the mammal, wherein the transfected progenitor cells of red blood cells produce altered red blood cells containing the protein which is non-native to

red blood cells in vivo in the mammal, and wherein the protein which is non-native to red blood cells is contained only in the altered red blood cells, and thereafter the protein which is non-native to red blood cells is released into blood stream of the mammal through rupture of the altered red blood cells.

Hollis et al is a deficient reference because Hollis et al fail to teach Applicant's claimed delivery mechanism which utilizes rupture of the red blood cells for delivering produced protein into blood stream in vivo. Most importantly, Hollis et al teach away from the Applicant's claimed invention. As discussed above, Hollis et al confirmed experimentally that the protein delivery mechanism of their expression system is cell secretion. Therefore, Hollis et al teach that the natural result flowing from the operation as taught would result in the performance of secretion. This teaching is contrary to Applicant's claimed invention which utilizes the rupture of the cell to deliver protein.

The Examiner agrees that Hollis et al do not teach that the red blood cells should lyse and release the protein into the blood. However, the Examiner alleges lysis of red blood cells is an inherent property, therefore, Hollis et al anticipates the Applicant's claims. Applicant respectfully disagrees.

Applicant specifically discussed in the Specification as filed and restated in Paper No. 6 that there are two known pathways for proteins to export from the cells after their production. The first pathway is secretion. The second pathway is exocytosis. Both processes are natural processes of protein exportation. Applicant's claimed invention is materially different from these two processes and delivers the expressed proteins into blood stream through red blood cell rupture.

As held by the Court in In re Weiss, 26 USPQ 2d 1885, 1888 (Fed. Cr. 1993):

> The mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency]...[which requires that] the disclosure is sufficient to show that the natural results flowing from the operation as taught would result in the performance of the questioned function.

Nothing in Hollis et al would teach one skilled in the art that the natural result

flowing from the Hollis et al's protein secretion mechanism would result in Applicant's claimed protein delivery by the rupture of red blood cells. On the contrary, one skilled in the art would not view the natural results of Hollis protein exportation to be by cell rupture because the protein would have previously been secreted from the cell.

Hollis et al's teaching relies solely on cell secretion for protein delivery regardless the expression systems. It is apparent from Hollis et al's teaching that rupture of red blood cells has not been utilized for a mechanism of protein delivery by the instant prior art. With respect to inherency, W.L. Gore Associates Inc. v. Garlock, 220 USPQ 303, 314 (Fed Cir. 1983), cert. Denied, 469 U.S. 851 (1984) stands for the principal that inherency may be relied upon only where the consequence of following the reference disclosure always inherently produces or results in the claimed invention. In the present situation, the consequences of following Hollis et al. does not always produce or result in Applicant's claimed invention because in Hollis et al. the protein is secreted from the cell. Hollis et al. distinctly point out (Column 8, lines 14-15) and demonstrate with their strong experimental evidence (Examples 3 and 4) that the protein is secreted in red blood cells and is not released by the rupture of the cell.

In addition, Hollis et al cannot be found to disclose Applicant's claimed red blood cell rupture by virtue of its inherency because one of ordinary skill in the art viewing the Hollis et al reference teaching secretion of protein would not understand that the unmentioned mechanism of protein delivery by red blood cell rupture can be present in the Hollis et al reference.

For the reasons given above, Hollis et al fail to anticipate Applicant's claimed invention. Accordingly, Applicant respectfully requests withdrawal of the rejection based upon 35 USC §102(b).

9. Response to Rejection of Claims 1, 6, 7, 16, 20 and 21 based upon 35 U.S.C. §103 (a)

Claims 1, 6, 7, 16, 20 and 21 stand rejected under 35 U.S.C. §103 (a) as being unpatentable over Hollis et al (US Patent 5,538,885) in view of Schlegel (US Patent 5,576,206) and Wickham et al (US Patent 5,846,782). This rejection is respectfully

traversed.

Claim 1 and 16 are independent claims with different claim limitations. Claim 1 of the present invention is a method for producing and delivering protein in vivo. More specifically, the method is to produce altered red blood cells containing protein which is non-native to red blood cells, and using altered red blood cell rupture to deliver produced the protein which is non-native to red blood cells into blood stream in vivo. Claim 16 of the present invention is a method using a hemoglobin promoter to produce altered red blood cells containing non-hemoglobin protein, and using altered red blood cell rupture to deliver produced non-hemoglobin protein into blood stream in vivo. As discussed previously, the claimed method of the present invention for delivering protein in vivo bypasses the two natural protein exportation pathways. Instead, the claimed method utilizes red blood cell rupture, as the mechanism to deliver desired proteins into the blood stream.

Hollis et al's teaching has been discussed above. The deficiencies of Hollis et al are not overcome by Schlegel and Wickham et al.

Schlegel teaches a process of immortalizing cells to produce immortalized cell lines. Further, Schlegel teaches that the immortalized cells are either actual functional sites of the gene expression product, or they export the product through secretion, which is contrary to Applicant's claimed invention.

Wickham teaches a chimeric adenovirus fiber protein, vectors that comprise the chimeric adenovirus fiber protein, and the methods of constructing and using such vectors. Wickham's teaching provides improved vectors and methods for cell targeting. However, Wickham's teaching only addresses efficiency of protein production by improving vectors and methods for cell targeting, it does not address protein delivery after its production.

Both Schlegel and Wickham et al. fail to teach producing a non-native protein to red blood cells, or using hemoglobin promoter to produce non-hemoglobin proteins only in the progenitor cells of red blood cells, and delivering the gene expression product into blood stream in vivo through rupture of red blood cells.

Viewing all the teachings of the prior art, the inventive concept of Applicant's claimed invention is missing. Consequently, using retroviral or adenoviral vectors by

Schlegel and using lentiviral vector by Wickham for gene expression are not relevant to Applicant's claimed invention. Therefore, the deficiencies of Hollis et al are not overcome by the Examiner's picking and choosing of selected teachings from the additional references of Schlegel and Wickham.

In conclusion, viewing all the teachings of the prior art presented, one of ordinary skill in the art would not have expected to be able to modify or combine Hollis, Schlegel, and Wickham references to obtain Applicant's claimed invention.

On the other hand, it has been a long felt need for solutions to the problem of production and delivery of protein in vivo. New strategies and methods to overcome difficulties in achieving the goals of producing and delivering proteins in vivo are strongly in demand. The fact that lack of teaching in the art, either patents or scientific publications, on using Applicant's approach for protein production and delivery in vivo strongly indicates unobviousness of Applicant's claimed invention. Therefore, Applicant firmly believes that Applicant's claimed invention is unobvious in view of the prior art. Accordingly, Applicant respectfully requests withdrawal of the rejection based upon 35 U.S.C. §103(a).

It is respectfully submitted that Claims 1-8, 10-21 and 24-29, the remaining pending claims, are now in condition for allowance and such action is respectfully submitted. Applicant's Agent respectfully requests direct telephone communication from the Examiner with a view toward any further action deemed necessary to place the application in final condition for allowance.

10/28/2002
Date of Signature

By: _____

Yi Li
Registration No. 44,211
Agent for Applicant
Telephone: (786) 242-9349

Address correspondence to:
CUSPA Technology Law Associates
11820 SW 107 Avenue
Miami, FL 33176

Specification With Changes Noted

Page 6, Paragraph 3

The proteins that may be synthesized and delivered by the method of the present invention include, but are not limited to, an antibody, an enzyme, a cofactor, an interferon, a hormone, and a peptide. Furthermore, the proteins include natural proteins, fusion proteins, and mutated proteins.

Page 6, Paragraph 8

Another object of the present invention is to use a hemoglobin promoter to achieve the control of the expression and synthesis of proteins in the precursors of the red blood cells. In addition, another object is to use the strength of the hemoglobin promoter to promote efficiency of the protein synthesis.

Page 10, Paragraph 3

Using the method of the present invention, a protein is produced by the progenitor cells of the red blood cells, and carried by the red blood cells for delivery. Once the red blood cells that carry the protein release into the peripheral blood, the red blood cells themselves have no ability to further express protein. The red blood cells are the temporary storage sites for the protein until the protein is released out when the red blood cells rupture. This is a major distinction between red blood cells and other nucleated blood cells. The [later] latter is capable of protein expression in the peripheral blood.

Page 10, Paragraph 4 which continues on Page 11

Second, the red blood cells provide a natural protection to the protein against degradation. The protein is only contained in the red blood cells because the

hemoglobin promoter is active only in the progenitor cells of the red blood cells. Red blood cells do not have a nucleus. Hence, the produced protein will not be degraded by nuclear enzymes. Compared to other nucleated cells, such as white blood cells, the protein will be more stable in the red blood cells. An example [Example] of the protein stability in the red blood cells is demonstrated by natural hemoglobin through the life cycle of red blood cells. In addition, the red blood cells also protect the proteins from extra-cellular environment before the proteins enter into the blood circulation.

Page 11, Paragraph 2

Third, the method of the present invention provides an efficient protein delivery mechanism. Natural red blood cells have a half life about 60 days in peripheral blood. Therefore, by utilizing red blood cell rupture as the delivery mechanism the protein supply will be continuous and constant. For certain diseases, for instance, [hemaphilia] haemophilia and hormone related diseases, continuous protein supply is desired. For other diseases, such as cancer, a constant protein supply not only provide a treatment, but may also contribute to the prevention of the disease. Furthermore, in some cases although a constant protein supply may not be the mode of natural supply, it could be therapeutic and beneficial. A suitable example of such case is insulin supply of diabetes patients.

Page 12, Paragraph 1

Fifth, with the method of the present invention, the amount of protein production and delivery can be controlled by the amount of host cells collected and treated. When the stem cells are collected from bone marrow, the treated bone marrow can be implanted at the original collection position, or enclosed in a [sag] bag, then implanted back into a patient's bone marrow. If a large quantity of protein is needed, such as human serum albumin, the amount of protein production can be controlled by the numbers of transplant sites. If a patient inherits a genetic defect and needs a continuing supply of the normal gene product throughout life, a permanent implantation

could be selected. If only short term activity of a gene is needed, such as to activate the immune system against cancer cells or an infectious agent, the [sag] bag can be taken out from the body when the therapy is complete, or no longer desired.

Page 13, Paragraph 1

The method of the present invention has a broad spectrum of applications, particularly suitable for gene [argumentation] augmentation therapy, in which a healthy gene replaces the product of a missing or defective gene but does not physically replace the flawed DNA itself. An example of gene therapy using the method of the present invention is to treat a haemophilia patient. In this case, a retroviral vector will be constructed with a hemoglobin promoter and haemophilia factor XIII gene. Then, an amount of bone marrow is collected from the patient and the stem cells is transduced with the vector. The vector construction and gene transduction can be accomplished using procedures known in the art. The bone marrow after treatment then is transplanted back into the patient. After transplantation, the transduced stem cells will produce blood cells. The haemophilia factor XIII will be produced only in the red blood cells which will circulate in the peripheral blood of the patient under treatment. At the end of life cycle of these red blood cells, haemophilia factor XIII will be released into bloodstream upon the rupture of the red blood cells. Because of a continuous generation of red blood cells by the transduced stem cells and continual red blood cell rupture at the end of their life cycle, the patient under such therapy will have continuous supply of haemophilia factor XIII.

Claims With Changes Noted

Please amend Claims 1, 10, 13-16, 24 and 27-29 to:

1 (Twice Amended). A method for producing and delivering protein in vivo comprising the steps of:

(a) inserting into a vector a promoter which is active only in progenitor cells of red blood cells, and a gene encoding a protein which is non-native to red blood cells, wherein said promoter and said gene are operably linked; [inserting a promoter and a gene encoding a non-native protein to red blood cells in a vector with an operable linkage between said promoter and said gene; wherein said promoter is active only in progenitor cells of red blood cells];

(b) collecting an amount of progenitor cells of red blood cells from a mammal;

(c) transfecting said progenitor cells of red blood cells in vitro with said vector containing said promoter and said gene;

(d) introducing the [treated] transfected progenitor cells of red blood cells back to said mammal, wherein the [treated] transfected progenitor cells of red blood cells produce altered red blood cells containing [and] said protein which is non-native to red blood cells in vivo in said mammal, and wherein said protein which is non-native to red blood cells is contained only in said altered red blood cells, and thereafter said protein which is non-native to red blood cells is released into blood stream of said mammal through rupture of said altered red blood cells.

10 (Twice Amended). The method of Claim 1 wherein the rupture of said altered red blood cells in vivo is induced by genetic mutation, wherein [life time] the lifetime of said altered red blood cells is modified.

13 (Twice Amended). The method of [any one of Claim 11-12] either one of Claims 11 or 12 wherein said protein which is non-native to red blood cells is a naturally occurring protein.

14 (Once Amended). The method of [any one of Claim 11-12] either one of Claims 11 or 12 wherein said protein which is non-native to red blood cells is a fusion protein.

15. (Once Amended) The method of [any one of Claim 11-12] either one of Claims 11 or 12 wherein said protein which is non-native to red blood cells is a mutated protein.

16. (Twice Amended). A method for producing and delivering protein in vivo comprising the steps of:

(a) inserting into a vector a hemoglobin promoter and a gene encoding a non-hemoglobin protein [in a vector with an operable linkage between said promoter and said gene]; wherein said promoter and said gene are operably linked;

(b) collecting an amount of host progenitor cells of red blood cells from a mammal;

(c) transfecting the host cells in vitro with said vector containing said hemoglobin promoter and said gene;

(d) introducing the [treated] transfected host cells back to said mammal, wherein the [treated] transfected host cells produce altered red blood cells containing [and] said non-hemoglobin protein in vivo in said mammal, and wherein said non-hemoglobin protein is contained only in said altered red blood cells, and thereafter said non-hemoglobin protein is released into blood stream of said mammal through rupture of said altered red blood cells.

24 (Twice Amended). The method of Claim 23 wherein the rupture of said altered red blood cells in vivo is induced by genetic mutation, wherein [life time] the lifetime of said altered red blood cells is modified.

27 (Twice Amended). The method of [any one of Claim 25-26] either one of Claims 25 or 25 wherein said non-hemoglobin protein is a naturally occurring protein.

28. (Once Amended) The method of [any one of Claim 25-26] either one of Claims 25 or 26 wherein said non-hemoglobin protein is a fusion protein.

29. (Once Amended) The method of [any one of Claim 25-26] either one of Claims 25 or 26 wherein said non-hemoglobin protein is a mutated protein.